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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
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ART UNIT	PAPER NUMBER
1615	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/540,139	COLOMBO ET AL.	
	Examiner	Art Unit	
	Jeffrey T. Palenik	1615	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *21 June 2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Remarks

The Examiner thanks Applicants for the timely reply filed 12 March 2008, in the matter of 10/540,139.

Applicants' election **without traverse** of Group I, claims 1-10, in the reply filed on 12 March 2008 is acknowledged.

The remaining claims of Group II (11-20) are hereby withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

The remaining claims 1-10 are presented and represent all claims under consideration.

Information Disclosure Statement

An Information Disclosure Statement (IDS), filed 21 June 2005 is acknowledged and has been reviewed.

Specification

The abstract of the disclosure does not commence on a separate sheet in accordance with 37 CFR 1.52(b)(4). A new abstract of the disclosure is required and must be presented on a separate sheet, apart from any other text.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Dependent claim 6 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim contains subject matter that is not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Claim 6 is drawn to a method limitation wherein the step is carried out in a container constituted of "dielectric material". While the Examiner acknowledges that the term "dielectric material" is mentioned in the instant specification, the term is not defined by the instant specification in a clear and concise manner. Applicants provide a single "preferred" example for said material in the form of polytetrafluoroethylene loaded with carbon (see pp. 3 and 6 in Applicants' spec.) and it is unclear what other materials Applicants' define as part of the invention. As such, the disclosure of the instant specification is not sufficient to support the generic concept of "dielectric material" and requires further clarification. As construed in the prior art, the Examiner is interpreting the term "dielectric material" as a material which conducts electricity poorly, but supports an electrostatic field (see www.whatis.techtarget.com).

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "massively" in claim 1 is a relative term which renders the claim indefinite. The term "massively" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The parameter which is rendered indefinite by use of the above term is the degree to which the drug is dispersed within the particles. In view of Applicants' special definition for the term "massively dispersed (or in-bulk)" (see pg. 4, *Detailed Description*, ¶3), the Examiner broadly and reasonably interprets

the term as "mixed". Applicants' definition defines carrier particles having the drug deposited both on the inside and surface of the carrier particles.

The term "it" as recited in line 3 of claim 1 renders the claim indefinite because it is unclear to what the term refers, for instance, does "it" refer to the drug, the carrier, or the drug/carrier combination? Given Applicants' description (i.e. ¶1 of the *Detailed Description*, pg. 4), the Examiner broadly and reasonably interprets, the term "it" as referring to the drug.

The phrase "present in amorphous form in a quantity greater than or equal to 50%", as recited in lines 3-4 in claim 1, renders the claim indefinite because it is unclear as to what part of the composition formed comprises 50% or more of the amorphous form (i.e. 50% of what?). The above limitation is broadly and reasonably interpreted by the Examiner as the percent of drug which exists in the amorphous state (%A), which is defined by Applicants as being equivalent to 100% - %C, where (%C) is defined as the percent of residual crystallinity (see pg. 11, section 4, ¶2).

The phrase "loaded with" as recited in claim 7 renders the claim indefinite because it is not clear what the structural or chemical relationship is between PTFE and graphite. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonable interprets the phrase as "mixed together" or "admixed".

The term "sparingly" in claim 10 is a relative term which renders the claim indefinite. The term "sparingly" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The parameter in the claim which is rendered indefinite by the use of the above term is the degree to which a given drug is soluble in water. Herein, and for the purposes of examination on the merits, the Examiner broadly and reasonably interprets the term "sparingly" as a "solubility equal to or less than 100 μg of solute per 1 mL of solvent" (see *Materials Science and Engineering*; **Intro**.).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3 and 6-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Bergese et al. (see *Materials Science and Engineering*).

The instant claims are drawn to a process for preparing a composite containing a drug, which is 50% or more in the amorphous state, dispersed in an organic carrier, wherein the steps comprise forming a mixture of the drug and the carrier and irradiating the mixture using modulated microwave power such that the mixture is heated to a temperature which is higher than the melting point of the drug and said temperature is maintained for at least 5 minutes. Claims 2 and 3 further limit the method of step a), claim 1, to adding water as a solvent. Claims 6 and 7 further limit the irradiation container to being constituted of the dielectric material polytetrafluoroethylene (PTFE) loaded with graphite. Claim 8 further limits the irradiation step to a power range of 100-5,000 watts (W) for an overall time up to 120 minutes. Claims 9 and 10 both further limit the cross-linked polymer and drug, respectively.

Bergese et al. teach a process for preparing a nanocomposite composition via microwave processing which makes insoluble drugs soluble (Abstract; Introduction). "Sparingly" soluble drugs such as nifedipine or ibuprofen (i.e. drugs from Class II of Biopharmaceutical Classification System) are micronized in one of two types of carrier matrices; cross-linked polyvinylpyrrolidone (e.g. crospovidone), β-cyclodextrin or undecahydrate polymorphic modified β-cyclodextrin (*Materials and Methods, ¶1*). Table 1 presents crystallization data for irradiated samples of nifedipine (see samples PNf1 and PNf2). PNf2 is a wet mixture (e.g. slurry) sample preparation wherein fluid mixtures of solids in powder form with the solvent water (see pg. 794, left col.). A multimode Weflon reactor is used with a total processing time of 25 minutes wherein temperature of 175°C is reached in 15 minutes and maintained for 10 minutes. The result of which is a residual crystallinity ratio (RCR%) of less than 6%. As discussed above, Applicants' claimed percentage is 50% or greater of the drug in the amorphous state or %A ≥50%. Applicants' employ the RCR percentage into the calculation of %A wherein it is equal to 100% -

%RCR. Thus both PNf1 and PNf2 samples demonstrate a %A of >94%. Single- and multimode microwave reactors are taught which comprise Weflon™, which is a graphite loaded Teflon with the property of being highly microwave (MW) absorbent (*Materials and Methods*, ¶2). The multimode container which is used in the experiment is an Ethos MicroSYNTH applicator provided by Milestone, which per Table 1 is used for a duration of 25 minutes per nifedipine sample and per mechanical specifications, will deliver a forward-projected microwave field between 1,000 to 1,600 watts of power (see www.milestonesci.com).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-10 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bergese et al. (see *Materials Science and Engineering*) in view of Miyamoto et al. (WO 97/06781).

The instant claims are directed to a process for preparing a partially amorphised drug/carrier composite, as discussed above. Claim 4 recites a limitation to the amount of

water solvent which may be added to the dry mixture of the composite. Claim 5 further limits the pressure at which irradiation is carried out to a range of between 1-20 bar.

The teachings to Bergese et al. are discussed above. Bergese et al. additionally teaches that the pressures at which the samples are irradiated vary between 0.02 atmospheres (0.02 bar; per www.onlineconversion.com) and ambient pressure (p_a). The "pressure" component of Standard Temperature and Pressure (STP) is defined as 1.013 bar (IUPAC and Answers.com). However, the ambient temperature pressure value (e.g. STP) is not taught with the wetted sample (e.g. PNf2). Thus, the pressures at which any of the samples are irradiated are not expressly taught within the claimed range of 1-20 bar. Nor is the amount of water which is added to the dry mixture to prepare the practiced slurry by Bergese expressly taught.

Miyamoto et al. teach in Example 1, a mixture of 5 grams of water (i.e. 5 mL of water), 10 grams of nifedipine, 10 grams of succinic acid and 20 grams of hydroxypropylmethylcellulose-acetate succinate (HPMC-AS). The resulting mixture comprises 0.11 mL of water per gram of dry mixture.

Miyamoto et al. do not expressly teach irradiating any preparations at any specific or atmospheric pressures.

In view of the combined teachings of the prior art, one of ordinary skill in the pharmaceutical or biomedical art, at the time of the invention, would have been motivated to combine a drug, a carrier and a water solvent, admix them together and irradiate the mixture under specific microwave criteria to achieve the claimed amorphous composite. Such would have been obvious in the absence of evidence to the contrary since both Bergese and Miyamoto teach overlapping components (e.g. nifedipine, crospovidone, water) and variations to their respective methods, which can be incorporated into the instant process claims. Though the high-frequency dielectric heating is not expressly taught as being conducted in a container comprised of a dielectric material such as graphite-PTFE,

microwave heating using a microwave zone is especially preferable (col. 7, lines 29-46) and Example 4 teaches that the composition of Example 1 was heat-treated for 20 minutes at 700 W resulting in an amorphous solid dispersion.

A person of ordinary skill in the art would have a reasonable expectation of success in modifying the preparation process practiced by Bergese et al. using the solvent variations taught by Miyamoto et al. since the combined teachings disclose the instantly claimed composite preparation method.

Neither of the references expressly teach the process using the irradiation pressure range, as claimed by Applicants. Since the values and formats of each parameter with respect to the claimed composition are adjustable, it follows that each is a result-effective parameter that a person having ordinary skill in the art would routinely optimize. Optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ. As discussed earlier, microwave irradiation of the dry mixture is conducted at ambient pressure of 1.013 bar whereas the "wetted" mixture is irradiated at 0.02 bar. Thus, it would have been customary for an artisan of ordinary skill, to not only adjust the amount of water admixed with the dry components, but also to adjust the pressure at which the samples were irradiated in order to achieve the desired amount of residual crystallinity ratio. Thus, absent some demonstration of unexpected results from the claimed parameters, optimization of any of these parameters would have been obvious at the time of Applicants' invention.

All claims have been rejected; no claims are allowed.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey T. Palenik whose telephone number is (571) 270-1966. The examiner can normally be reached on 7:30 am - 5:00 pm; M-F (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Michael Woodward can be reached on (571) 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jeffrey T. Palenik/
Examiner, Art Unit 1615

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615